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Recurrent Pneumomediastinum and Pneumothorax in Langerhans Cell Histiocytosis

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Pneumothorax is an unusual complication of pulmonary Langerhans cell histiocytosis. We report three children who developed recurrent intrathoracic air leaks. In one case, bilateral pneumothoraces may have been precipated by intermittent positive pressure ventilation during general anaesthesia. Chemical pleurodesis was unsuccessful in preventing recurrence of pneumothoraces in two children. The use of extracorporeal membrane oxygenation as an alternative to intermittent positive pressure ventilation in children with respiratory failure from Langerhans cell histiocytosis is discussed. Med. Pediatr. Oncol. 29:139–142, 1997.

Key words: pneumothorax; Langerhans cell histiocytosis; ECMO

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a reactive disorder characterised by the infiltration of either single or multiple organ systems with proliferating cells bearing the phenotypic markers of epidermal Langerhans cells [1]. Lung involvement occurs in up to half of all children with multisystem disease and usually parallels overall disease activity [2]. Isolated pulmonary disease has been described in children but is more commonly found in young adults [3–6]. The natural history and prognostic significance of lung involvement by LCH is not well understood. Spontaneous pneumothorax (PTX) occurs in approximately 10% of children with pulmonary disease and may prove to be a terminal event [2,4,5]. In adults, recurrent PTXs follow the development of ''honeycomb lung'' and carry a poor long-term prognosis [7,8]. We report three children with multisystem LCH who suffered repeated intrathoracic air leaks with very different outcomes.

CASE REPORTS

Patient A

This male infant presented at 9 months with fever, weight loss and tachypnoea. On examination he had a disseminated skin rash previously diagnosed as molluscum contagiosum infection which had progressed despite treatment with gamma interferon. His chest X-ray (CXR) revealed bilateral reticular shadowing with multiple air cysts. A staphylococcal pneumonia was diagnosed and his clinical condition improved with intravenous antibiotics. A skin biopsy was performed which was diagnostic of LCH showing diffuse infiltration of the dermis with a mixed cell population including histiocytes which contained Birbeck granules on electron microscopy. Despite treatment with methylprednisolone (30 mg/kg for 3 days) followed by weekly injections of vinblastine (6 mg/m^2) his CXR appearances remained largely unchanged [9]. At 1 year of age, he was admitted with fever and tachypnoea secondary to a spontaneous left-sided PTX which was successfully drained. Repeated unilateral air leaks prevented removal of the chest drain for 8 days. Following this acute episode, his CXR remained abnormal with several large cystic areas present bilaterally and he was treated with a 5-day course of prednisolone (2 mg/kg) repeated at 28-day intervals in addition to weekly vinblastine. Twenty months later, steroids have been successfully withdrawn and his CXR shows considerable improvement.

Patient B

This boy presented at 16 months of age with a 4-month history of fluctuating skull lesions. Biopsy of an osteolytic area revealed sheets of large pale-staining cells with abundant pale cytoplasm and grooved nuclei. Electron microscopy revealed Birbeck granules consistent with a diagnosis of LCH. No evidence of involvement of any other system was seen and his skeletal lesions resolved with a short course of prednisolone (2 mg/kg). Attempts to wean him from prednisolone were accompanied by a recurrence of his skull lesions and he re-

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Fig. 1. CXR from patient B showing bilateral nodular shadowing and a pneumomediastinum as a result of LCH lung disease. There is an expansile lesion at the anterior end of the left first rib.

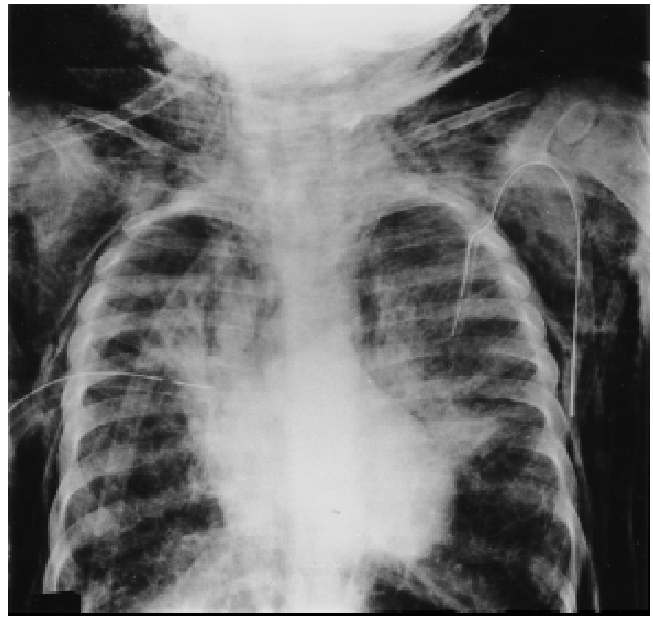

Fig. 2. CXR from patient B during his final illness. The ring shadows visible on the previous film have increased in diameter. Chest drains have been inserted bilaterally and there is extensive subcutaneous emphysema.

mained on an alternate day dose. Fifteen months after presentation, he began to complain of chest pain which corresponded with the appearance of an osteolytic lesion at the anterior end of the first rib. CXR revealed bilateral diffuse reticulonodular shadowing consistent with pulmonary involvement by LCH. No additional therapy was given and he continued to receive prednisolone (0.25 mg/kg) on alternate days. Four months later he was admitted with abdominal pain at which time physical examination revealed subcutaneous air in his neck and right chest wall. A pneumomediastinum was apparent on CXR (Fig. 1). He was treated with three doses of methylprednisolone (30 mg/kg) followed by maintenance hydrocortisone (50 mg administered at six hourly intervals) and weekly vinblastine (6 mg/m^2) [9]. Five days later, he developed a left-sided spontaneous PTX which was successfully drained. The next 10 days saw a gradual deterioration in his condition with recurrent bilateral PTXs, persisting pneumomediastinum and a pneumopericardium (Fig. 2). He became oxygen-dependent and developed a pyrexia which did not respond to treatment with broad spectrum antibiotics.

In an attempt to stabilize his respiratory function, he was anaesthetised for insertion/repositioning of chest drains and pleurodesis. Immediately following induction of anaesthesia, he had a prolonged asystolic cardiac arrest and although resuscitation was successful he required continuing ventilatory support (IPPV). Despite induced paralysis, his oxygen requirements continued to increase and in order to reduce his need for high pressure IPPV, he was started on extracorporeal membrane oxygenation (ECMO). Venovenous ECMO was instituted allowing the peak inspiratory ventilatory pressure to be reduced, thus preventing further intrathoracic air leaks. Tetracycline was instilled into both pleural spaces via chest drains to stimulate a chemical pleurodesis. Following his prolonged cardiorespiratory arrest, there was concern about his neurological status. Repeated clinical examinations indicated a developing spastic tetraplegia, and abnormal cortical activity was demonstrable on successive EEGs. ECMO was withdrawn after 2 weeks and respiratory support continued using only standard IPPV. This was accompanied by further PTXs and progressive carbon dioxide retention. After full discussion with the family, respiratory support was withdrawn and he died 24 hours later.

Patient C

A 13-year-old boy presented with a 3-month history of ''floating teeth'' secondary to osteolytic lesions in his mandible. Biopsy of this area revealed S-100-positive mononclear cells with eosinophillic cytoplasm consistent with LCH. Further investigation revealed cranial diabetes insipidus and short stature. There was no evidence of disease in any other system. MRI of the pituitary region was normal, CXR and pulmonary function tests were unremarkable. His initial treatment consisted of desmopressin, methylprednisolone (30 mg/kg) reducing to prednisolone (2 mg/kg) daily and vinblastine (6 mg/m^2) weekly. This regimen produced a radiological improvement in his mandible with stabilisation of the overlying teeth. Prednisolone was withdrawn after 3 months, although a total of 6 months of vinblastine therapy was administered. One year after presentation he developed a unilateral aural discharge and a LCH skin rash which were resistant to both prednisolone and vinblastine. Fur-

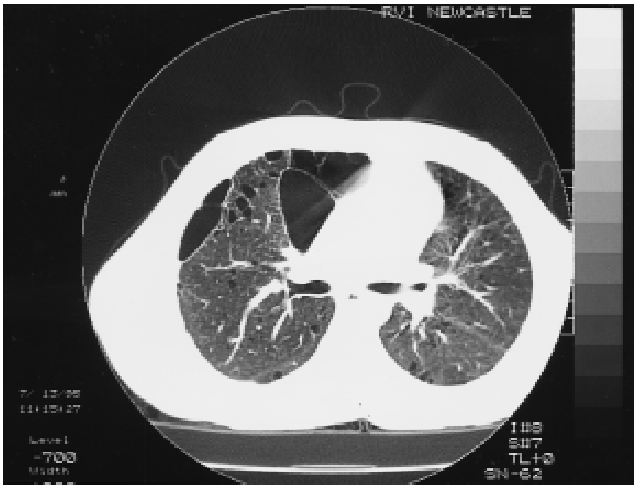

Fig. 3. CT scan of the lungs of patient C following bilateral pleurectomy. Large apical cysts and multiple smaller bullae are present bilaterally.

ther osteolytic lesions developed in his mandible and he was referred for extraction and curettage of all involved mandibular teeth. His CXR remained normal and his prednisolone dose was gradually reduced. Dental extraction proceeded uneventfully under antibiotic and steroid cover. He was electively paralysed and ventilated during the procedure. Forty-eight hours later, he developed severe left-sided chest pain and collapsed. On arrival at hospital, he was deeply cyanosed and tachypnoeic. CXR revealed bilateral PTXs present on a background of multiple lung bullae. Two chest drains were inserted and his condition improved. Following transfer to the regional cardiothoracic unit, he underwent a right apical pleurectomy using a video thoracoscopic approach. He was readmitted shortly after discharge with a spontaneous left-sided PTX and a partial left-sided pleurectomy was performed. Despite these procedures, he continued to have recurrent PTXs (a total of eleven independent episodes) and bilateral pleurectomies were performed via a median sternotomy. Following surgery, vinblastine and prednisolone were continued for 4 months. In the year following this procedure, no further PTXs have occurred although a CT scan of his chest reveals persisting bullae (Fig. 3). His pulmonary function tests continue to slowly improve but reveal a persisting restrictive defect and an abnormally small lung volume.

DISCUSSION

Young children with multisystem LCH often present with nonspecific symptoms such as failure to thrive, fever, irritability and loss of appetite [10]. Lung, liver and bone marrow failure may follow and are accompanied by a high mortality [11]. Pulmonary involvement does not necessarily indicate a poor outcome and spontaneous remission has been well documented at all stages of the disease [2,12]. CXR appearances in children with lung disease are those of reticulonodular shadowing secondary to interstitial alveolar infiltration by Langerhans cells [13]. Adults with primary pulmonary histiocytosis have more coarse infiltrates, particularly in the upper and midzones with characteristic sparing of the costophrenic angles. Hilar lymphadenopathy is unusual [14]. Disease progression is accompanied by the appearance of small cysts and bullae with subsequent fibrosis and ''honeycombing'' [15]. Spontaneous PTXs are thought to arise from the rupture of these cysts. PTXs occur more frequently in adult cases, who often have isolated progressive lung disease [3].

There are no specific recommendations for the treatment of PTX from LCH described in the literature and management follows established principles using underwater sealed drainage. The small number of cases presenting at individual centres has prevented the formation of a consensus view towards the timing and importance of pleurodesis and thoracotomy in treatment. Whilst PTXs improved with drainage alone in a single patient, a variety of physical methods were attempted in an effort to obliterate the pleural space in the other two children. Chemical pleurodesis with tetracycline was unsuccessful in patient B and further PTXs were prevented by the introduction of ECMO. In the remaining patient, PTXs could only be avoided by bilateral pleurectomy. Concern that total pleurectomy would compromise the possibility of future lung transplantation led to patient C initially undergoing partial pleurectomies. These did not prevent further PTXs and open total pleurectomy was performed bilaterally to good effect. We conclude that nonsurgical measures may be inadequate and that total pleurectomy, rather than pleurodesis, should be considered in the setting of recurrent PTXs secondary to LCH.

In retrospect, it seems likely that had ECMO been instituted earlier in the management of patient B, it may have prevented the pulmonary damage produced by high-pressure IPPV. To our knowledge, ECMO has not previously been used in the management of LCH lung disease (ELSO Registry, Ann Arbor, MI). Whilst ECMO was technically successful in reducing the requirement for IPPV and thus avoiding high inspiratory pressures which would have produced further air leaks, its use can only be justified in the presence of a potentially reversible cause of respiratory failure. The use of other ventilatory techniques including high frequency membrane oscillation or ''jet ventilators'' has not been reported.

To our knowledge, PTX has not previously been described as a postoperative complication of children with LCH. In this case preoperative CXRs were unremarkable and no pulmonary involvement had been detected previously. Pulmonary function tests had been performed only once (at diagnosis) and were normal. It is likely that IPPV during the operation induced the development of multiple lung bullae which subsequently ruptured. This

suggests that patient C had preexisting pulmonary disease which was undetectable on CXR. His lung involvement only became symptomatic following IPPV during a seemingly uneventful general anaesthetic. We suggest that more sensitive means of detecting LCH lung involvement, such as high-resolution CT scanning and/or pulmonary function testing, may be useful in patient assessment prior to general anaesthesia [16]. If at all possible, IPPV should be avoided in children with active LCH, as this may exacerbate previously unrecognized lung disease. If general anaesthesia is unavoidable, it should not be carried out as a day case procedure and should be followed by a postoperative CXR.

All children received systemic therapy for LCH. Patients A and C were treated with weekly vinblastine and courses of prednisolone for an acute worsening of the disease on an ''as required'' basis. Patient B received ''induction'' with methylprednisolone followed by weekly vinblastine in accordance with LCH 1 (treatment schedule 1) [9]. In patient B, pulmonary involvement was first seen as an incidental finding on CXR, and because of its asymptomatic nature, further systemic therapy, in addition to alternate day prednisolone, was not instituted. A conservative approach to the therapy of asymptomatic multisystem LCH has been advocated by others [17]. Following this experience we would consider an early trial of vinblastine and prednisolone in pulmonary disease, symptomatic or not, although whether this would have changed the eventual outcome in this case is uncertain. In view of the improved lung disease we observed in patient A when treated with prednisolone, we chose to continue steroids in patient B until he was established on ECMO. Corticosteroids were then withdrawn in case they prevented successful pleurodesis. The long-term outcome of LCH lung disease is unpredictable and whether its course can be altered by systemic therapy remains uncertain. Radiological improvement has been documented in adults treated with prednisolone [16,18]. Whether corticosteroids, rather than any other systemically administered agent, are particularly effective in the treatment of paediatric LCH lung disease is unknown. Assessing the benefits of any therapy is difficult because of the possibility of spontaneous improvement [12]. Studies suggesting that PTXs are associated with a poor prognosis are derived from adult data and may not be relevant to childhood LCH [7,8]. Patient A continues to make excellent progress with both clinical and radiological improvement in his condition.

PTX is a potentially fatal complication of LCH which occurs in approximately 10% of children with pulmonary involvement [2] and may only be controlled by bilateral total pleurectomy. It is our experience that the nature of the underlying lung disease makes recurrent PTXs the rule rather than the exception. Early consideration of ECMO may be advantageous in a child whose respiratory function is deteriorating as a result of numerous PTXs. We suggest that general anaesthesia be undertaken with caution in children with active LCH, as IPPV may produce bullae formation with a sudden deterioration in lung function.

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